PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/000770	26.02.2004	26.02.2003

International Patent Classification (IPC) or both national classification and IPC
C12Q1/68

Applicant
SOLEXA LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/000770

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/000770

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4,6
	No:	Claims	1-3,5,7-13
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 02/053778 A (DAVIS SCOTT ; GENOMICFX INC (US); GREGG KEQIN (US); REUS BONNIE (US);) 11 July 2002 (2002-07-11)
D2: WO 01/57248 A (SOLEXA LTD) 9 August 2001 (2001-08-09)
D3: WO 02/061127 A (BALASUBRAMANIAN SHANKAR ; BARNES COLIN (GB); KLENERMAN DAVID (GB); SOL) 8 August 2002 (2002-08-08)
D4: EP-A-0 195 277 (HOECHST AG) 24 September 1986 (1986-09-24)
D5: US-A-5 476 930 (GRYAZNOV SERGEI M ET AL) 19 December 1995 (1995-12-19)
D6: KWOK P-Y: "METHODS FOR GENOTYPING SINGLE NUCLEOTIDE POLYMORPHISMS" 2001, ANNUAL REVIEW OF GENOMICS AND HUMAN GENETICS, ANNUAL REVIEWS, US, PAGE(S) 235-258 , XP001153175 ISSN: 1527-8204

1. The present application does not meet the criteria of **Article 33(1) PCT**, because the subject-matter of **claims 1 - 3, 5, 7 - 13** is not new in the sense of **Article 33(2) PCT**.

1.1 The document **D1** discloses the subject-matter of **claims 1 - 3, 5, 7 - 13** on pages 3 - 12, 15 and 16, figure 1 and examples 1 - 4.

2. The present application does not meet the criteria of **Article 33(1) PCT**, because the subject-matter of **claims 1 - 14** does not involve an inventive step in the sense of **Article 33(3) PCT**.

3. The document **D1** is regarded as being the closest prior art to the subject-matter of **claims 1 - 14** and discloses a method for genotyping nucleic acids, whereby two oligonucleotides, namely a reporter oligonucleotide and a capture oligonucleotide hybridize to a target oligonucleotide. The reporter oligonucleotide hybridizes to the specified target oligonucleotide immediately adjacent to the capture oligonucleotide. The first, capture, and reporter oligonucleotides are subjected to ligation conditions, in which the capture oligonucleotide is ligated to the reporter oligonucleotide only if the 3'-terminal nucleotide

is complementary to the corresponding nucleotide of the first oligonucleotide. Different capture oligonucleotides ligated with reporter oligonucleotides are attached at different distinguishable addresses. Capture oligonucleotides ligated with reporter oligonucleotides are attached at the distinguishable addresses, such that different capture/reporter oligos will be attached at different addresses. The method takes place on a bioarray, and the capture oligonucleotide can be attached to the distinguishable address directly or indirectly, care in particular for paragraph on "Hybridization attachment embodiment" but also for pages 3 - 12, 15 and 16 as well as for figure 1 and examples 1 - 4. The codes leading to the proper targeting of the ligated strands to their specific address on the microarray are hereby referred to as zipcode-oligonucleotides.

4. The subject-matter of **claims 1 - 14** therefore **differs** with respect to the closest prior art **D1** in that the identification of the variant site is done by a sequencing reaction, said sequencing reaction being primed by a secondary structure, namely a hairpin oligonucleotide, and said hairpin oligonucleotide being comprised in the two oligonucleotides ligated together in the event of complementarity to the variant site, e.g. to the single nucleotide polymorphism.

6. The **problem to be solved** by the present invention may therefore be regarded as providing a different means of identifying the variant site of the genetic location in question, e.g. a single nucleotide polymorphism.

7. The solution proposed in **claims 1 - 14** of the present application cannot be considered as involving an inventive step (**Article 33(3) PCT**) for the following reasons.

8. Prior art **D2** states on page 3, summary of the invention, that one of the aims of the invention is the realisation, that sample preparation and sequence analysis procedures can be improved, if the target polynucleotide is maintained in spatial relationship to the primer. This is achieved by linking primer and target "via a bond stronger than that of hybridization". On page 5 this embodiment is specified to be a hairpin loop structure, whereby the 3' end of the hairpin serves a polymerase reaction / sequencing reaction.

9. Prior art **D3**, like **D2**, also introduce said feature, c.f. page 6, second paragraph to page 7, line 25.

10. Dependent **claim 11** does not contain any features which, in combination with the features of any claim to which it refers, meet the requirements of the **PCT** in respect of

novelty and/or inventive step. **Claim 11** claims the fragmentation of the sample genomic DNA prior to contacting the oligonucleotides. This embodiment is anticipated on page 6, second paragraph of prior art **D2**, as well as on page 6, line 30 to page 7, line 5 of prior art **D3**.

11. **D4**, **D5** and **D6** anticipate the non-enzymatic chemical linking of oligonucleotides by means of 5'-iodide and 3'-selenophosphate (**claims 13** and **14** of the underlying application), c.f. the whole documents.

12. The solution proposed in **claims 1 - 14** of the present application cannot be considered as involving an inventive step (**Article 33(3) PCT**), since the features / embodiments not anticipated in **D1** - c.f. the embodiments of claims 11, 13 and 14 - are merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed. The skilled in the art would combine prior art documents **D1** and **D2** and arrive at the teachings of the underlying application. Therefore, the present application does not meet the criteria of **Article 33(1) PCT**, because the subject-matter of **claims 1 - 14** does not involve an inventive step in the sense of **Article 33(3) PCT**.